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Title : New diphenylurea compounds

Art Unit : 1624

Examiner : Emily BERNHARDT

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.132

I, Mark MILLAN, a citizen of the United Kingdom, of 19, rue du Président Wilson, 78230 LE PECQ, France, declare and say that :

I hold the degree of Bachelor of Arts (1978), Master of Arts (1983), and Doctor of Sciences (1985) from the University of Cambridge (England).

Since 1995, I have been Director of the Division of Psychopharmacology at the Institut de Recherches Servier, France.

I am the author or co-author of more than 500 international publications such as patents, scientific publications and communications.

I am one of the co-inventors of US Patent Application Serial n° 09/896,278 filed June 29, 2001 concerning "New diphenylurea compounds".

I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological data contained in application, which were performed either by me or under my supervision. I also fully support the conclusions derived and the arguments presented as concerns the therapeutic interest of the compounds described.

The compounds of the present invention have pharmacological properties that allow their use in the treatment of disorders of the central nervous system.

Throughout this declaration, we are presenting a substantial number of publications concerning the actions of α_2-**adrenoceptor** or **5-hydroxytryptamine2C** (5-HT_{2C}) receptor antagonists in tests presented in application Serial n° 09/896,278 (see former Declaration), and their prediction of the potential of the treatment of i) sexual dysfunction and libido, ii) schizophrenia, iii) cognitive function and iv) sleep disorders.

i) Sexual dysfunction and libido:

Extensive evidence for the utility of α_2-**adrenoceptor** antagonists in reducing sexual dysfunction, for example the selective agent yohimbine, has been documented:

1- "Evidence for the modulation of sexual behavior by **α-adrenoceptors** in male rats", J.T. Clark, E.R. Smith, J.M. Davidson, *Neuroendocrinology*, 41, 36-43 (1985);

2- "Double-blind trial of yohimbine in treatment of psychogenic impotence", K. Reid, et al., *The Lancet*, 421-423 (1987);

3- "**Alpha$_2$-adrenoceptor** antagonists and male sexual behavior: I. Mating behavior", E.R. Smith et al., *Physiology and Behavior*, 41, 7-14 (1987);

4- "Pharmacological analysis of male rat sexual behavior", D. Bitran, E.M. Hull, *Neuroscience and Biobehavioral Reviews*, 11, 365-389 (1987);

5- "Assessment of erectogenic properties of apomorphine and yohimbine in man", P. Danjou et al., *British Journal of Clinical Pharmacology*, 26, 733-739 (1988);

6- "Effect of yohimbine hydrochloride on erectile impotence: a double-blind study", J.G. Susset et al., *the Journal of Urology*, 141, 1360-1363 (1989);

7- "Double blind trial of yohimbine hydrochloride in the treatment of erection inadequacy", A.J. Riley et al., *Sexual and Marital Therapy*, 4, 1, 17-26 (1989);

8- "Yohimbine and naloxone: effects on male rat sexual behavior", I. Koskinen et al., *Psychology and behavior*, 50, 589-593 (1991);

9- "Fluoxetine-induced sexual dysfunction and an open trial of yohimbine", F.M. Jacobsen, *Journal of Clinical Psychiatry*, 53, 4, 119-122 (1992);

10- "Effect of yohimbine-trazodone on psychogenic impotence: a randomized, double-blind, placebo-controlled study", F. Montorsi et al. *Urology*, 44, 5, 732-736 (1994);

11- "Effectiveness of yohimbine in the treatment of erectile disorder: four meta-analytic integrations", M.P. Carey, B.T. Johnson", *Archives of Sexual Behavior*, 25, 4, 341-360 (1996);

12- "Double-blind, placebo-controlled safety and efficacy trial with yohimbine hydrochloride in the treatment of nonorganic erectile dysfunction", H.G. Vogt et al., *International Journal of Impotence Research*, 9, 155-161 (1997)

13- "Is high-dose yohimbine hydrochloride effective in the treatment of mixed-type impotence? A prospective, randomized, controlled double-blind crossover study", P. Kunelius et al., *Urology*, 49, 3, 441-444 (1997);

14- "Yohimbine in erectile dysfunction: the facts", A. Morales, *International Journal of Impotence Research*, 12, S70-S74 (2000);

As further **α-2 adrenoceptor** antagonist pentolamine (Vasomax), also improves sexual dysfunction:

15- "Oral phentolamine: an alpha-1, **alpha-2 adrenergic** antagonist for the treatment of erectile dysfunction", Golstein et al., *International Journal of Impotence Research*, 12, Suppl 1, S75-S80 (2000);

16- "Vasomax for the treatment of male erectile dysfunction", Golstein et al., *World Journal of Urology*, 19, 51-56 (2001).

There is also evidence for utility of **5-HT$_{2C}$** receptor antagonists in the treatment of sexual dysfunction:

17- "The role of the **5-HT$_2$** receptor in the regulation of sexual performance of male rats", M.M. Foreman et al., *Life Sciences*, 45, 1263-1270 (1989);

18- "DOI-induced inhibition of copulatory behavior in male rats: reversal by **5-HT$_2$** antagonists", N.V. Watson, B.B. Gorzalka, *Pharmacological Biochemistry and Behavior*, 39, 605-612 (1991);

19-"Clozapine acts as a **5-HT$_2$** antagonist by attenuating DOI-induced inhibition of male rat sexual behavior", T. Klint, K. Larsson, *Psychopharmacology*, 119, 291-294 (1995);

20-"5-HT$_{2A}$ and **5-HT$_{2C}$** Serotonin receptors differentially modulate sexual arousal and the hypothalamo-pituitary-testicular response to the presence of a female", N.K. Popova, T.G. Amstislavskaya, *Neuroendocrinology*, 76, 28-34 (2002).

ii) ***Schizophrenia:***

Recent articles have provided evidence for the use of **5-HT$_{2C}$** receptors antagonist properties of schizophrenic patients in the treatment independent of dopaminergic mechanism:

21-"**5-HT$_2$** Receptor antagonism reduces hyperactivity induced by amphetamine cocaine, and MK-801 but not D_1 agonist C-APB", M.F. O'Neill et al., *Pharmacology Biochemistry and Behavior*, 63, 2, 237-243 (1999);

22-"Attenuation of haloperidol-induced catalepsy by **5-HT$_{2C}$** receptor antagonist", C Reavill et al., *British Journal of Psychopharmacology*, 126, 572-574 (1999);

23-"Inverse antagonist activity of atypical antipsychotic drugs at human **5-hydroxytryptamine2C** receptors", K. Herrick-Davis et al., *The Journal of Pharmacology and Experimental Therapeutics*, 295, 1, 226-232 (2000);

24-"**5-HT$_{2C}$** Receptor antagonist: potential in schizophrenia", M.D. Wood et al., *Drug Development Research*, 54, 88-94 (2001);

25-"RNA Editing of **5-HT$_{2c}$** receptor is reduced in schizophrenia", M.S. Sodhi et al., *Molecular Psychiatry*, 6, 373-379 (2001);

26-"Ritanserin antagonism of m-chlorophenylpiperazine effects in neuroleptic-free schizophrenics patients: support for serotonin-2 receptor modulation of schizophrenia symptoms", W. Abi-Saab et al., *Psychopharmacology*, 162, 55-62 (2002).

Others groups have emphasized the important role of **α_2-adrenoceptor** blockade in treating schizophrenic and suppressing extrapyramidal motor symptoms. For example:

27-"Enhanced cortical dopamine output and antipsychotic-like effects of raclopride by **alpha2 adrenoceptor** blockade", P. Hertel et al., *Science*, 286, 105-107 (1999);

28-"Idazoxan and response to typical neuroleptics in treatment-resistant schizophrenia: comparison with the atypical, neuroleptic, clozapine", R.E. Litman et al., *British Journal of Psychiatry*, 168, 571-579 (1996)

iii) ***Cognitive function:***

Evidence for significance of α_2-adrenoceptors in etiology of Alzheimer's disease, and for the utility of **α_2-AR antagonists** for the improvement of cognitive attentional function, has been well-established, for example for "idazoxan":

29-"Idazoxan, an **α_2-antagonist**, facilitates memory retrieval in the rat", S.J. Sara, V. Devaugues, *Behavioral and Neural Biology*, 51, 401-411 (1989);

30-"The effects and after effects of the **α_2-adrenoceptor** antagonist idazoxan on mood, memory and attention in normal volunteers", A.P. Smith et al., *J. Psychopharmacol.*, 6, 3, 376-381 (1992) [ref 29 cited in former declaration];

31-"The α_2 **antagonist** idazoxan remediates certain attentional and executive dysfunction in patients with dementia of frontal type", J.T. Coull et al., *Psychopharmacology*, 123, 239-249 (1996);

only from some beneficial loss in memory

but also others selective **α_2-adrenoceptors**, such as efaroxan, atipamezole and dexefaroxan:

32-"Loss of high-affinity **α_2-adrenoceptors** in Alzheimer's disease: an autoradiographic study in frontal cortex and hippocampus" J. Pascual et al., *Neuroscience Letters*, 142, 36-40 (1992);

agonist + not beneficial testing on 1 drug very early exp.

33-"The **α_2-adrenoceptor** antagonist, (+)-efaroxan, enhances acetylcholine release in the rat cortex in vivo", S. Telles, et al., *European Journal of Pharmacology*, 277, 113-116 (1995);

34-"Dose- and parameter-dependent effect of atipamezole, an **α_2-antagonist**, on the performance of rats in a five-choice serial reaction time task", J. Sirvio et al., *Pharmacology Biochemistry and Behavior*,

dealing w. attention deficit results very limited p. 124 p. 129

45, 123-129 (1993);

35-"Facilitation of cognitive functions by a specific **α_2-adrenoceptor** antagonist, atipemazole", A. Haapalinna et al. *European Journal of Pharmacology*, 347, 29-40 (1998);

36-"Effects of acute and subchronic administration of dexefaroxan, an **α_2-adrenoceptor** antagonist, on memory performance in young adult and aged rodents", P. Chopin et al., *The Journal of Pharmacology and Experimental Therapeutics*, 301, 1, 187-196 (2002).

Note the above mentioned importance of α_2-adrenergic receptor antagonism in enhancing cholinergic transmission, which favors cognitive function.

iv) ***Sleep disorders:***

Finally the **5-HT$_{2C}$** antagonist interacting with human sleep, it can play a prominent role in treatment of sleep disorders:

37-"Effects of ritanserin on sleep disturbances of dysthymic patients", T. Paiva et al., *Psychopharmacology*, 96, 395-399 (1988);

38-"Serotonin-2 receptors and human sleep: effect of a selective antagonist on EEG, power spectra", H.P. Landolt et al., *Neuropsychopharmacology*, 21, 455-466 (1999);

39-"Onlanzapine increases slow-wave sleep: evidence for blockade of central of **5-HT$_{2C}$** receptors in vivo", A.L. Sharpley et al., *Biological Psychiatry*, 47, 468-470 (2000);

40-"Effect of SB-243213, a selective **5-HT$_{2C}$** receptor antagonist, on the rat sleep profile: a comparison to paroxetine", M.I. Smith et al., *Pharmacological, Biochemistry and Behavior*, 71, 599-605 (2002).

Thus, *via* former Declaration filed 1/13/03, publications enclosed connected with "*Pharmacological study*" (pages 38-40) presented in Examples A-D, and "*Background of the invention*" (page 1, line 8 to page 2, line 17) of the present application, we can assume that compounds of US Serial n° 09/896,278 besides the fact they are usable in the treatment of depression, anxiety, Parkinson's disease, and impulsive behaviour disorders, they are usable in the treatment of schizophrenia, cognitive disorders, libido disorders and sexual dysfunction, and sleep disorders.

drug abuse ?

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of the title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

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Executed at : Courbevoie
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